REMARKS

Applicant has carefully reviewed and considered the Office Action mailed on December 30, 2003, and the references cited therein.

Applicant thanks the Examiner for the courtesy of a telephone interview on May 4, 2004. The Examiner and Applicant's representative, Robin A. Chadwick, took part in the interview. Another representative of the Applicant had intended to be present during the interview but was unable to attend. Applicant apologizes for any inconvenience that this may have caused the Examiner. During the interview, the pending claims and the art cited in the December 30, 2003 Office Action were discussed but no agreement was reached on these issues. This account is believed to be a complete and accurate summary of the interview as required by 37 C.F.R. § 1.133. If the Examiner believes that this summary is inaccurate or incomplete, Applicants respectfully request that the Examiner point out any deficiencies in his next communication so that Applicants can amend or supplement the interview summary.

Applicant has amended the specification to reflect a claim of priority to U.S. Patent 6,344,316 filed June 25, 1997 and to PCT Application No. PCT/US97/01603 filed January 22, 1997. Applicant submits that this claim of priority is properly made under 37 C.F.R. § 1.78(a)(5)(ii)(A) because the present application was filed prior to November 29, 2000 and each of the present inventors are named inventors of both U.S. Patent 6,344,316 and PCT Application No. PCT/US97/01603. An unsigned Declaration reflecting this priority claim is provided herewith. Applicant will provide a signed Declaration shortly.

Claims 1-19 are now pending in this application. New claim 19 has been added. Support for "identifying the mutation's location and type" in new claim 19 is present throughout the specification, for example, at page 15, lines 10-14. Support for "wherein each probe type in the probe arrays occupies a predefined region of less than 1 mm^2" in new claim 19 is present throughout the specification, for example, at page 8, line 28 to page 9, line 3 and at page 29, lines 23-27. Support for "wherein the target polynucleotide sequence is not known" in new claim 19 is present in the specification, for example, at page 10, line 27 to page 11, line 4. Support for "wherein hybridizing is performed at an appropriate stringency for selection of perfectly-matched duplexes" can be found throughout the specification, for example, at page 12, lines 6-29. Applicant submits that the subject matter of claim 19 is supported by the specification as filed and that such amendment adds no new matter.

§102(b) Rejection of the Claims

Claims 1-4, 6-10, 12-15 and 17 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by PCT Application No. PCT/US97/01603 (WO 97/27317) by Lockhart et al. Applicant submits that in view of the claim of priority to PCT Application No. PCT/US97/01603 this reference is not prior art. Applicant requests withdrawal of this rejection under 35 U.S.C. § 102(b).

§102(e) Rejection of the Claims

Claims 1-4, 6-10, 12-15 and 17 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent 6,344,316 by Lockhart et al. Applicant submits that in view of the claim of priority to U.S. Patent 6,344,316 filed June 25, 1997, this reference is not prior art. Applicant requests withdrawal of this rejection under 35 U.S.C. § 102(e).

§103(b) Rejection of the Claims

Claims 5 and 16 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over WO 97/27317 by Lockhart et al. in view of Cantor et al. (U.S. Patent 5,631,134). Claims 5 and 16 are directed to the methods of the invention wherein the overhangs have free 3'-ends. According to the Examiner, while Lockhart et al. do not teach overhangs with free 3' ends, Cantor does provide this teaching at col. 12, lines 9-19.

Applicant submits that in view of the amended priority claim provided herein, WO 97/27317 by Lockhart et al. is not prior art. Moreover, as described in more detail below, U.S. Patent 5,631,134 does not disclose or teach the invention. Applicant therefore requests withdrawal of this rejection under 35 U.S.C. § 103(a).

§103(a) Rejections of the Claims

The Examiner has also rejected Claims 11 and 18 under 35 U.S.C. § 103(a) as allegedly unpatentable over WO 97/27317 to Lockhart et al. in view of Southern (U.S. 5,700,637). Claims 11 and 18 are directed to the method of the invention wherein the arrays are arranged in parallel. According to the Examiner, while Lockhart et al. do not teach arrays arranged in parallel, Southern does provide this teaching at col. 7, lines 12-22.

Applicant submits that in view of the amended priority claim provided herein, WO 97/27317 by Lockhart et al. is not prior art. Moreover, as described in more detail below, U.S. Patent 5,700,637 does not disclose or teach the invention. Applicant therefore requests withdrawal of this rejection under 35 U.S.C. § 103(a).

The Examiner has also rejected claims 1-18 under 35 U.S.C. § 103(a) as allegedly unpatentable Cantor et al. (U.S. 5,631,134, filed June 5, 1995) in view of Southern (U.S. 5,700,637, filed April 19, 1994) and Lipshutz et al (U.S. 6,300,063, filed November 29, 1995).

Claim 1 is directed to a method of determining the presence of a mutation in a target polynucleotide, comprising the steps of: (a) providing at least two identical polynucleotide probe arrays, each array comprising probes, wherein each probe comprises a double stranded region and a single-stranded n-mer overhang region such that the overhangs in each array constitute a complete set of n-mers; (b) hybridizing the target polynucleotide to said overhangs of probe polynucleotides in one array to generate a target hybridization pattern; (c) hybridizing a reference polynucleotide to said overhangs of probe polynucleotides in a second array to generate a reference hybridization pattern; and (d) determining the presence of a mutation in the target polynucleotide by normalizing intensity differences of hybridized probes in the reference and target hybridization patterns, comparing intensity differences of probes in the reference and target hybridization patterns and determining whether a mutation is present in the target polynucleotide.

Claim 12 is directed to a method of determining whether two or more target polynucleotides are identical, comprising the steps of: (a) providing at least two identical polynucleotide probe arrays, each array comprising probes, wherein each probe comprises a double stranded region and a single-stranded n-mer overhang region such that the overhangs in each array constitute a complete set of n-mers; (b) hybridizing first target polynucleotide to said overhangs of probe polynucleotides in one array to generate a first hybridization pattern; (c) hybridizing second target polynucleotide to said overhangs of probe polynucleotides in a second array to generate a second hybridization pattern; and (d) normalizing intensity differences of hybridized probes in the first and second hybridization patterns, comparing intensity differences of probes in the first and second hybridization patterns and determining whether two or more target polynucleotides are identical.

Claims 2-11 depend from claim 1 and claims 13-18 depend from claim 12. Applicant submits that so long as the cited references do not disclose or teach the subject matter of claims 1 or 12, then claims 2-11 and 13-18 are patentable in view of those cited references.

Moreover, applicant submits that new claim 19 is patentable so long as the cited references do not disclose or teach the subject matter of claims 1 or 12, because claim 19 is directed to similar subject matter.

The above rejections under 35 USC § 103(a), with respect to the other references cited, are respectfully traversed. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference teachings to as to arrive at the claimed method. Second, the art must provide a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations (M.P.E.P. § 2143). The teaching or suggestion to arrive at the claimed method and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure (M.P.E.P. § 2143 citing with favor, *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)).

Applicant submits that a *prima facie* case of obviousness cannot be established from the combination of cited references because the references do not teach all the claim elements, there is no suggestion or motivation to combine the references so as to arrive at the claimed methods, and there is no reasonable expectation of success that the references could produce the claimed methods.

Failure to Disclose All Elements

Applicant submits that the references fail to disclose or teach all the claimed elements. In particular, the combination of references fails to teach hybridizing target and reference polynucleotides to two identical polynucleotide probe arrays, comparing intensity differences of probes in the reference and target hybridization patterns and determining whether a mutation is present in the target polynucleotide. As conceded by the Examiner, Cantor et al. (U.S. Patent 5,631,134) do not teach hybridizing a reference polynucleotide to a second array and determining the presence of a mutation by comparing the reference and target hybridization patterns. Office Action at 3 (June 26, 2003). The Examiner has stated that Southern (U.S. Patent

5,700,637) teaches hybridizing a reference polynucleotide to a second array and determining the presence of a mutation by comparing the reference and target hybridization patterns, and cites to column 7, lines 10-31 of the Southern reference. Office Action at 3 (June 26, 2003). However, at column 7, lines 10-31, Southern only describes analyzing several sequences simultaneously. No mention of a reference polynucleotide or of comparing reference and target or first and second hybridization patterns is made at column 7, lines 10-31, or elsewhere, in the Southern reference. Instead, Southern simply contemplates testing a series of test samples. Finally, Lipshutz et al (U.S. 6,300,063), describes methods that employ arrays having internal controls such as perfect match and mismatch probes. Lipshutz does not teach separately hybridizing target and reference polynucleotides to two identical polynucleotide probe arrays. Hence, none of the cited references teach hybridizing target and reference polynucleotides to two identical polynucleotide probe arrays, comparing intensity differences of probes in the reference and target hybridization patterns and determining whether a mutation is present in the target polynucleotide.

Other elements are also missing from the cited references. For example, Southern does not disclose that each probe comprises a double-stranded region and a single-stranded n-mer overhang region (see e.g., col. 7, lines 2-9; col. 8, line 59 to col. 9, line 35; and Examples 1-2, describing synthesis and use of a single-stranded oligonucleotide on CPG or glass supports). Moreover, Southern does not disclose or teach hybridizing the target or reference polynucleotide to probes having such double stranded and single-stranded overhangs.

Applicant also submits that the combination of references cited by the Examiner fails to effectively teach use of a complete set of n-mers. As is appreciated by one of skill in the art from the teachings of the present application, use of such a complete set of n-mers permits analysis of an unknown polynucleotide. Analysis of polynucleotides by the present invention does not require knowledge of the sequence(s) of the target polynucleotide. However, such knowledge is required to practice prior art methods such as those described in Cantor et al. (U.S. Patent 5,631,134) in view of Southern (U.S. Patent 5,700,637) and/or Lipshutz et al (U.S. Patent 6,300,063).

For example, the arrays disclosed by Lipshutz (U.S. Patent 6,300,063) are designed as customized arrays for detecting polymorphisms in only certain target genes (not all genes).

Lipshutz et al. is not directed to the presently claimed methods that use arrays having complete sets of n-mers.

While Southern may have identified several problems relating to generating and utilizing arrays with complete sets of n-mers, Southern does not solve these problems. For example, Southern teaches that a large number of sequence combinations are needed to analyze a sequence, but does not solve the problem of generating and using an array with a complete set of n-mers that would involve such a large number of sequence combinations. See U.S. Patent 5,700,637 at col. 4, lines 14-46. Southern does not describe how to analyze unknown sequences despite the section entitled "Analysis of an Undetermined Sequence," for example, because Southern asserts in this section that the full sequence of a nucleic acid need not be determined. See U.S. Patent 5,700,637 at col. 3, lines 34-63.

Cantor et al. teach away from the use of a complete set of n-mers, first, by describing how hard it would be to make an array with such a large number of probes (see, e.g., col. 6, lines 6-13), second, by explicitly stating that the set of probes need not contain every possible combination of nucleotide sequences (see, e.g., col. 6, lines 14-17), and third, by failing to teach how to make such a complete set of n-mer probes, as described in more detail below. Even in the Summary of the Invention, Cantor et al. explicitly states that the single-stranded region of the probes comprises every possible combination of sequences *over a predetermined range*, meaning that not all sequences are represented in the probes but only those in *a predetermined range.*

Hence, the combination of references cited fails to teach use of a complete set of n-mers and hybridization of a target and reference polynucleotides to two identical polynucleotide probe arrays, comparing intensity differences of probes in the reference and target hybridization patterns and determining whether a mutation is present in the target polynucleotide

No Reasonable Expectation of Success

The Cantor et al. reference, the Southern (U.S. 5,700,637) and Lipshutz et al (U.S. 6,300,063) references do not provide a reasonable expectation of success of generating an array having a complete set of n-mers that can successfully be used in the methods of the invention. To render an invention obvious, the combination of the cited art must teach or suggest the claimed invention and provide a reasonable expectation of success in preparing the claimed invention. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); *In re O'Farrell*, 853

F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988). Applicant submits that even when combined, one of skill in the art would not have a reasonable expectation that the teachings of Cantor, Southern and Lipshutz could successfully prepare an array with a complete set of n-mers that could be used in the claimed methods for determining the presence of a mutation in a target polynucleotide, or determining whether two or more target polynucleotides are identical.

One of skill in the art could not reasonably expect from the confusing and speculative teachings of Cantor et al. (U.S. Patent 5,631,134) to produce an array with a complete set of n-mers that could successfully work in the methods of the present invention. In particular, Cantor et al. provide no disclosure of an actual hybridization procedure that yields any sequence information whatsoever for a nucleic acid. For example, Cantor et al. describes a single synthesis of a single pool of 5-mers consisting of variable bases (N_5) whose sequences are unknown (Example 2). These small molecular weight 5-mers are separated from the plasmid used for their synthesis, linked to biotin and then attached to a streptavidin-coated surface. Hence, the "array" made according to Cantor et al. is simply a mixture of oligonucleotides whose sequences and locations on a solid support are unknown. Cantor et al. explicitly state:

> The initial array containing about a thousand probes. The particular sequence at any location in the array will not be known.

Cantor et al. (U.S. Patent 5,631,134) col. 13, lines 14-16. According to Cantor et al., "identification of particular elements of the array" is accomplished by hybridization with known nucleic acid sequences. *Id.*, col. 13, lines 19-21. Thus, if the "array" provided by Cantor et al. has about 1000 different probes, about one thousand different hybridization reactions would therefore have to be performed in order to identify the sequence of each probe in the array. The tedium and inefficiency of such repeated hybridization procedures would in itself undermine the expectations one of skill in the art might have of successfully generating and then productively using an array having a complete set of n-mers.

Furthermore, Applicant submits that the array described by Cantor et al. could not reasonably survive intact during the 1000 or more hybridization reactions needed to establish the identity and location of each probe in a 5-mer (or larger) n-mer array. As is known to one of skill in the art, single-stranded probes are prone to nuclease digestion, and such nucleases can be present in contaminated or improperly handled reagents and as well as in samples of nucleic acids (e.g., targets used as known nucleic acids for determining the 5-mer sequences). Even if

the skilled artisan successfully guarded against nuclease digestion, the 1000 or more cycles of heating and exposure to hybridization solutions would tend to degrade the Cantor et al. "array" and thereby undermine its utility for its intended purposes.

Hence, Cantor et al. utilizes the term "determinable" (i.e., unknown but theoretically identifiable) with reference to the probe sequences throughout U.S. Patent 5,631,134. See col. 3, lines 58-59; col. 5, line 52; col. 6, line 57; col. 8, line 6; col. 8, line 27; col. 9, line 4. Applicant submits that such "determinable" probe "arrays" that have no known sequences and no identified positions also have no practical utility for sequence analysis applications. An array cannot be used for sequencing unless the sequence and location of each probe on an array is known without a doubt. One of skill in the art could therefore receive no guidance whatsoever from the "determinable" arrays of the Cantor et al. disclosure that would lead to the already determined arrays and methods of the invention.

Moreover, even if one of skill in the art did perform one thousand different hybridization reactions, Applicant submits the separate single 5-mer probes on the Cantor et al. "array" could not be reliably identified, located or even detected by such hybridization reactions. While there may be more than one oligonucleotide of the same sequence in such an "array," Cantor et al. does not teach how to cluster the same-sequence oligonucleotides into a single location (or "feature") as provided in the present application. As is known to one of skill in the art, it is almost impossible to detect hybridization between a single nucleic acid and its complement, especially when the nucleic acid is as short as five nucleotides -- one of skill in the art simply cannot attach enough label molecules to a single complementary nucleic acid to allow reliable location of a single 5-mer probe attached to the "array" provided by Cantor et al. This may be why the only actual data provided in Cantor et al. is a graph of the ratio of radioactive counts after a "hot wash" versus a "cold wash" from a pool of probes attached to beads (Example 13, Fig. 12A). Neither the location nor sequence of the probes in an array is needed to generate the data provided by Cantor et al. in Fig. 12A.

Applicant submits that use of terms "array" and "sequencing" by Cantor et al. is misleading because Cantor et al. do not teach how to make an array with any useful features that would permit actual sequencing information to be obtained. Instead, Cantor et al. is limited to vague, confusing and hypothetical teachings that would not guide one of skill in the art to the present invention. The undetermined "arrays" described by Cantor et al. are thus not the arrays

described and claimed by the invention. Cantor et al. simply has not disclosed how to make a useful array of probes with known sequences at known locations, let alone a complete set of n-mers. Hence, Cantor et al. (U.S. Patent 5,631,134) fails to teach the methods of the invention that involve using arrays of probe features where the sequence and location of the probes in those features are known. Similarly, Cantor et al. fails to effectively teach arrays with complete sets of n-mers. Thus, Cantor et al. not only fails to provide a reasonable expectation of success but also fails to teach or suggest all the claim limitations (M.P.E.P. § 2143).

Similarly, as described above, Lipshutz et al (U.S. Patent 6,300,063) is directed to detection of polymorphisms in particular selected genes, and not to the presently claimed methods that use arrays having complete sets of n-mers. Hence, the arrays contemplated by Lipshutz are designed as customized arrays for detecting polymorphisms in only certain target genes (not all genes).

While Southern may have identified several problems relating to generating and utilizing arrays with complete sets of n-mers, Southern does not solve these problems. In particular, Southern describes "some statistics" at col. 4, lines 14-46, showing that a large number of sequence combinations are needed to analyze a sequence, but does not solve the problem of generating and using an array with a complete set of n-mers that would involve such a large number of sequence combinations. For example, in Example 1, Southern synthesizes only oligo-dT_{10}-oligo dT_{14} on a slide. In Example 2, Southern synthesizes only the following two oligonucleotides 3' CCC GCC GCT GGA (cosL) and 3' CCC GCC TCT GGA. In Examples 3 and 4, Southern synthesizes only the oligonucleotides shown in Table 1. In Example 6, only oligonucleotides relating to the wild type and mutant (sickle cell anemia) β-globin gene were used on a slide. In Example 7, Southern prepares a slide with 256 octapurines (eight nucleotide oligonucleotides with only adenine and guanine residues). Therefore, all of these examples generate discrete sets of oligonucleotides and do not come even come close to generating a complete set of n-mers.

Furthermore, the array fabrication techniques disclosed in Southern is not amenable to making an n-mer array suitable for the presently claimed invention. The Southern arrays are fabricated by separating features with rubber tubing. The tubes are glued to a glass plate at 8-mm intervals (see Example 3, col. 10, lines 15-28). The glass plate itself was 220 x 220 mm in size and allowed for a total of 78 different oligonucleotides (Table 1). As described by Southern at

col. 5, lines 5-22, when large genomes are analyzed the area required to manufacture arrays with a suitable number of features using the Southern techniques becomes prohibitory (e.g. 2500 pieces of film for the human genome). Clearly, Southern has not developed the technology needed for generating arrays with complete sets of n-mers.

Thus, Southern (U.S. 5,700,637) is limited to hypothetical discussions relating to an "Apparatus and Method for Analyzing Polynucleotide Sequences and Method of Generating Oligonucleotide Arrays." Southern provides no teaching on how to actually generate a usable array comprising a complete set of n-mer probes, how to actually perform a hybridization reaction that would actually distinguish single base mismatches and how to discriminate such single base mismatches from noise and non-mismatches once such a hybridization reaction has been performed.

No Motivation to Combine

Applicant submits that there is no motivation to combine the teachings of Cantor with the teachings of Southern and Lipshutz. One of skill in the art would not have been motivated to combine Cantor's undetermined arrays with Southern's single-stranded probes and Lipshutz's customized arrays to produce the presently claimed invention, particularly since, as discussed above, none of these references effectively teach the use of complete n-mer arrays to conduct the methods of the invention.

It is respectfully submitted that the Examiner is employing hindsight to arrive at Applicant's invention in the absence of any suggestion in the cited art to take Applicant's approach. The Examiner is reminded that it is impermissible to use Applicant's specification as a template to arrive at the conclusion that the claimed invention is obvious. *In re Fritsch*, 23 U.S.P.Q.2d 1780, 1782 (Fed. Cir. 1992). For example, it is improper to presume that Cantor et al. or Southern has the features or arrays described and claimed by the present invention when the evidence suggests otherwise. Similarly, it would be improper to presume that Lipshutz discloses a complete set of n-mers when the teachings of Lipshutz are clearly directed to detecting polymorphism in certain genes. Thus, it is improper, in determining whether a person of ordinary skill would have been led to the invention by this combination of references, simply to use that which the inventor taught against its teacher. *In re Lee*, 61 USPQ2d, 1430, 1434 (Fed. Cir. 2002).

Applicant submits that without hindsight at the time of the invention, no reasonable likelihood existed of combining Cantor et al. (U.S. 5,631,134), Southern (U.S. 5,700,637) and Lipshutz et al (U.S. 6,300,063) to produce the invention of the rejected claims. (See MPEP 2143.02 which mandates a reasonable likelihood of success in making the combination.) Cantor et al. and Southern fail to produce an array with a complete set of n-mers and provide only speculation as to how one might produce arrays with such large numbers of oligonucleotide probes. Cantor lacks the features of the invention and Southern fails to disclose probes that are both double-stranded and single-stranded. Lipshutz is explicitly limited to use of customized arrays having less than a complete set of n-mers for detected selected polymorphisms.

Finally, Applicant submits that none of the references disclose or teach the subject matter of claim 19 relating to identifying the mutation's location and type; wherein each probe type in the probe arrays occupies a predefined region of less than 1 mm^2; wherein the target polynucleotide sequence is not known; and wherein hybridizing is performed at an appropriate stringency for selection of perfectly-matched duplexes. In particular, the combination of cited references does not teach all of these claim elements, there is no suggestion or motivation to combine the references so as to arrive at the subject matter of claim 19, and there is no reasonable expectation of success that the references could produce the method of claim 19.

Hence, the combination of Cantor et al. (U.S. 5,631,134), Southern (U.S. 5,700,637) and Lipshutz et al (U.S. 6,300,063) does not produce the claimed invention. Applicant requests withdrawal of this rejection under 35 USC § 103(a) of claims 1-18.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date May 28, 2004

By Robin A. Chadwick
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CERTIFICATE UNDER 37 CFR § 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelop addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 28 day of May 2004

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